

**APPLICATION
FOR
UNITED STATES LETTERS PATENT**

Applicant(s): Samuel I. Achilefu
Joseph E. Bugaj
Richard B. Dorshow
Raghavan Rajagopalan

Title: TUMOR TARGETED PHOTODIAGNOSTIC-
PHOTOTHERAPEUTIC AGENTS

Assignee: Mallinckrodt Inc.

Beverly A. Lyman
WOOD, HERRON & EVANS, L.L.P.
2700 Carew Tower
441 Vine Street
Cincinnati OH 45202
(513) 241-2324

Attorney Docket No.: MRD-72

SPECIFICATION

0981271.101701
TUMOR TARGETED PHOTODIAGNOSTIC-
PHOTOTHERAPEUTIC AGENTS

TUMOR TARGETED PHOTODIAGNOSTIC-PHOTOTHERAPEUTIC AGENTS

Field of the Invention

This invention relates to novel dye-bioconjugates for use in diagnosis and therapy, particularly novel compositions of cyanine dye bioconjugates of bioactive molecules.

5 Background of the Invention

Cancer will continue to be a primary cause of death for the foreseeable future, but early detection of tumors would improve patient prognosis (R. T. Greenlee et al., Cancer statistics, 2000, *CA Cancer J. Clin.*, 2000, 50, pp. 7-33). Despite significant advances in current methods for the
10 diagnosis of cancer, physicians still rely on the presence of a palpable tumor mass. At this, however, the many benefits of early medical intervention may have been already compromised.

Photodiagnosis and/or phototherapy has a great potential to improve management of cancer patient (D. A. Benaron and D. K. Stevenson,
15 Optical time-of-flight and absorbance imaging of biologic media, *Science*, 1993, 259, pp. 1463-1466; R. F. Potter (Series Editor), *Medical optical tomography*:

- functional imaging and monitoring*, SPIE Optical Engineering Press, Bellingham, 1993; G. J. Tearney et al., In vivo endoscopic optical biopsy with optical coherence tomography, *Science*, 1997, 276, pp. 2037-2039; B. J. Tromberg et al., Non-invasive measurements of breast tissue optical properties using frequency-domain photon migration, *Phil. Trans. Royal Society London B*, 1997, 352, pp. 661-668; S. Fantini et al., Assessment of the size, position, and optical properties of breast tumors in vivo by non-invasive optical methods, *Appl. Opt.*, 1998, 37, pp. 1982-1989; A. Pelegrin et al., Photoimmunodiagnosis with antibody-fluorescein conjugates: in vitro and in vivo preclinical studies, *J. Cell Pharmacol.*, 1992, 3, pp. 141-145). These procedures use visible or near infrared light to induce the desired effect. Both optical detection and phototherapy have been demonstrated to be safe and effective in clinical settings and biomedical research (B. C. Wilson, Optical properties of tissues, *Encyclopedia of Human Biology*, 1991, 5, 587-597; Y-L. He et al., Measurement of blood volume using indocyanine green measured with pulse-spectrometry: Its reproducibility and reliability, *Critical Care Medicine*, 1998, 26, pp. 1446-1451; J. Caesar et al., The use of Indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function, *Clin. Sci.*, 1961, 21, pp. 43-57; R. B. Mujumdar et al., Cyanine dye labeling reagents: Sulfoindocyanine succinimidyl esters, *Bioconjugate Chemistry*, 1993, 4, pp. 105-111; U.S. Patent No. 5,453,505; Eric Hohenschuh, et al., Light imaging contrast agents, WO 98/48846; Jonathan Turner, et al., Optical diagnostic agents for the diagnosis of neurodegenerative diseases by means of near infra-red radiation, WO 98/22146; Kai Licha, et al., In-vivo diagnostic process by